REMARKS

Summary of Office Action

In the Office Action of October 18, 2007, the Examiner indicated that Claims 3 and 11 were objected to due to a typographical error. The Examiner rejected claims 1, 3, 7-8, 9-11, 17-23, 24-30 and 33 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,440,465 to Meisner (hereinafter "Meisner"), in view of U.S. Patent No. 6,358,542 to Cuomo et al. ("hereinafter "Cuomo"), and U.S. Patent Application Publication No. 20030108651 to Crea et al. (hereinafter "Crea"). The Examiner further rejected claims 26-28, 30-31 and 33 under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claims. The Examiner also indicated that two of the references cited on the information disclosure statement were not published because they did not correspond to published documents. No other issues were raised.

The prior response submitted on April 16, 2008 addressed the issues raised by the Examiner in the Office Action of October 18, 2007. The instant response is being filed to supplement this response with additional arguments and evidence as to the allowability of the instant claims.

Summary of Amendment

Upon entry of the present Supplemental Amendment, Claims 27-28 and 33 will have been amended, and claim 31 will have been cancelled. In particular, claim 27 is being amended herewith to narrow those cancers treated by the method to only those selected from the group consisting of leukemia, renal cell adenocarcinoma, breast ductal carcinoma, melanoma and colon cancer, which amendment is supported at least by Figure 5 of the originally filed specification. Claims 1, 3, 5-14, 16-30, 33, and 37-71 thus remain currently pending, with claims 12-14, 16 and 37-71 being in withdrawn status. By the present Amendment and Remarks, Applicants submit that the rejections have been overcome and respectfully requests reconsideration of the outstanding Office Action.

Statement of Substance of Interview

Applicants wish to sincerely thank the Examiner and her Supervisor for discussing in detail the merits of the case in the telephonic interview conducted on May 7, 2008. The 103(a) rejection of record over Meisner, Cuomo and Crea was discussed, and reasons for the nonobviousness of the instant invention over these references were provided. Also, the rejection of record of claims 26-28, 30-31 as lacking enablement for the full scope of claims was discussed, and Applicants sought to explain to the Examiner some of the history behind the development of the claimed treatment method and reasons why the administration of the compound as claimed for the treatment of various cancers would be understood by those of ordinary skill in the art to effect such treatment without requiring undue experimentation. Further discussion of the reasons for the non-obviousness and enablement of the claimed methods is provided in more detail below.

Applicants wish to note that they have sought to comply with the Examiner's suggestion in this telephonic conversation to narrow the scope of cancers treated by the method by amending claim 27 to recite treatment of only those cancers selected from the group consisting of leukemia, renal cell adenocarcinoma, breast ductal carcinoma, melanoma and colon cancer (i.e., only 5 different types of cancers), as shown for example in Figure 5 of the instant application.

Applicants remain very grateful to the Examiner for all of her assistance and advice, and sincerely thank the Examiner for the opportunity to present the supplemental arguments provided herein.

Applicant's Response

1. Status of Claims

Applicants respectfully reiterate, as stated in the Response previously submitted April 16, 2008, that while the Examiner has rejected claims 1, 3, 7-8, 9-11, 17-23, 24-30 and 33 under 3 U.S.C. 103(a) (*see*, e.g., Office Action page 3) and has rejected claims 26-28, 30-31 and 33 under 35 U.S.C. 112, first paragraph (*see, e.g.,* Office Action page 6), the Examiner has omitted any reasons for the rejection of claims 5-6 and 31, although the Office Action Summary sheet (PTOL-326) indicates that these claims are in rejected status.

Applicants therefore respectfully request that the Examiner provide the reasons for rejection, if any, of claims 5-6. The Examiner is reminded that any new statement of reasons for the rejection would be considered to be "new grounds" for the rejection, as no basis for the rejection of claims 5-6 has as-yet been provided. The Examiner is therefore precluded from making the next Action *final* on the basis of such grounds. See MPEP 706.07(a).

2. Information Disclosure Statement

The Examiner indicated that the last two documents cited in the IDS of November 14, 2006 were placed in the file but were not considered because they did not comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 in that "they are not a published document" (Office Action page 2.)

Applicants respectfully reiterate, as noted in the previous Response submitted on April 16, 2008, that 37 CRF 1.98 states that "(a) any information disclosure statement filed under § 1.97 shall include the items listed in paragraphs (a)(1), (a)(2) and (a)(3) of this section [including] (1) A list of all patents, publications, applications, or other information submitted for consideration by the Office." Thus, 37 CFR 1.98 indicates that publications, applications and "other information" may be submitted in an IDS form. Accordingly, the foreign Examination Reports cited in the IDS form are proper and should be considered by

the Examiner. Applicants respectfully request that the Examiner indicate consideration of the cited Examination Reports in the next Office Action.

3. Objection to Claims 3 and 11

The Examiner objected to claims 3 and 11 due to a minor typo-type error, namely the presence of an extra period in the claims. This typo-type error was corrected in the Response submitted April 16, 2008, and thus this objection is now believed to be moot.

4. Rejection of Claims 1, 3, 7-11, 17-30 and 33 under 35 U.S.C. 103(a) over Meisner, Cuomo and Crea

The Examiner rejected claims 1, 3, 7-11, 17-30 and 33 under 35 U.S.C. 103(a) over Meisner in view of Cuomo and Crea. In particular, the Examiner asserts that Meisner teaches administering oleuropein for the treatment of skin-conditions such as psoriasis, and mentions skin cancer as one of the conditions (*see, e.g.,* Office Action pages 3-4.) The Examiner also asserts that Cuomo teaches administering oleuropein for the treatment of cancer (*see, e.g.,* Office Action page 4) and asserts that Crea teaches different methods of administering oleuropein (*see, e.g.,* Office Action page 4.) This rejection is respectfully traversed.

Claim 1 is not obvious over the combination of Meisner, Cuomo and Crea, because none of the references teaches or suggests a method for treating cancer "selected from the group consisting of colon cancer, renal adenocarcinoma and melanoma" by administering a compound having the formula as claimed, such as, e.g., oleuropein.

Meisner teaches compositions for "the treatment of psoriasis and related skin ailments" (Abstract.) The "related skin ailments" taught by Meisner can include other chronic eczematous skin conditions such as atopic dermatitis (*see, e.g.,* column 6, lines 10-15.) Meisner further teaches that such a treatment composition can contain oleuropein, which is believed to have antioxidant properties useful in the treatment of psoriasis (*see, e.g.,* column 4, lines 40-65.)

However, Meisner *does not teach or suggest* the use of oleuropein or other compounds matching the claimed formula for the treatment of any of colon cancer, renal adenocarcinoma and/or melanoma. Instead, in the section to which the Examiner refers, Meisner generally describes conditions related to skin aging, including the thinning of the dermis with age, as well as the increased incidence of skin cancer with aging that is related to skin thinning (*see, e.g.,* column 3, lines 20-45). Meisner compares the incidence of skin cancer and psoriasis as a function of age *to speculate on the physiological role of glucosamine*, and not to somehow suggest that a compound suitable for the treatment of psoriasis would be capable of treating skin cancer (*see, e.g.,* column 4, lines 1-20.) In other words, any description regarding skin cancer on the part of Meisner is intended only for the purposes of describing what is understood about the physiological role of glucosamine, and *is not intended to teach or suggest that oleuropein or any other antioxidant could be used for the treatment of skin cancer*. Applicants note that a mere mention of skin cancer as a skin disorder in the reference does not constitute a teaching of a treatment therefor using the compounds as claimed. In fact, Meisner *teaches against* the method of the instant claims by teaching that psoriasis and skin cancer have *different etiologies*, in that "since psoriasis and atopic dermatitis may strike at a young age, psoriasis is clearly not related to only the thinning skin, in contrast to skin cancer and decreased skin immune response" (column 4, lines 5-10.) Thus, while Meisner teaches providing oleuropein for the treatment of psoriasis, Meisner does not teach or suggest providing oleuropein for the treatment of a cancerous condition, such as melanoma.

Applicants respectfully suggest that the Examiner appears to be conflating this *mention* of skin cancer on the part of Meisner with a teaching of actual *treatment* of skin cancer with the compositions taught therein. Applicants submit that this is clearly not the intent of Meisner, as is clear by considering the patent document in its entirety. In particular, it is noted that the title of the Meisner patent is "Topical Composition for the Treatment of Psoriasis and Related Skin Disorders", where the related skin disorders are defined as "[o]ther chronic eczematous skin conditions" (column 6, line 9) such as atopic dermatitis.

Further evidence of the fact that Meisner intended the composition only for the treatment of psoriasis and other eczematous skin conditions (i.e., *not* skin cancer) is given by the fact that the examples of treatment therein were performed on subjects having psoriasis (columns 9-11), and the claims recite the "treatment of psoriasis" (*see, e.g.,* claims 1 and 10). Thus, it is clear that the compositions of Meisner are for the treatment of *psoriasis*, not skin cancer, and a mere mention on the part of Meisner of skin cancer as it relates to the physiological process of aging cannot be construed as a teaching of such cancer with the psoriasis-treatment compositions taught therein.

Cuomo does not make up for the deficiencies of Meisner in that Cuomo also does not teach or suggest the treatment of skin cancer or other cancers with the compound as claimed. In the section to which the Examiner refers, Cuomo teaches that oleuropein is an anti-oxidant found in olive oil (*see, e.g.,* column 2, lines 25-45) and Cuomo further teaches that olive oil is believed to lower the incidence of heart disease and breast cancer (*see, e.g.,* column 1, lines 30-35.) Thus, Cuomo teaches that olive oil may help to *prevent breast cancer*, and that it is possible that the cancer prevention may be at least in part due to antioxidative effects from oleuropein. However, Cuomo also does not teach or suggest that oleuropein is capable of *treating cancer*, such as skin cancer, as claims. Accordingly, as neither Meisner nor Cuomo teach or suggest *treating cancer* with oleuropein or other compounds of formula I in claim 1, it is considered that the claimed method is patentable over the references because they fail to teach or suggest each and every limitation of the claim.

It is furthermore noted that one of ordinary skill in the art would understand that a composition that is suitable for the *prevention* of cancer is not necessarily suitable for the *treatment* of the same cancer. For example, while antioxidants may be believed to reduce the incidence of certain types of cancer, the mechanism by which antioxidants work to inhibit cancer occurrence may actually have deleterious effects in the *treatment* of existing cancer. As is known to those of ordinary skill in the art, antioxidants work to promote cell health by reducing the numbers and effects of damaging free radicals in a biological system. However, for a person already having cancerous cells, such cell health promoting compounds could

actually promote the growth and formation of the cancerous cells themselves. In fact, it is common practice for physicians to warn patients prior to chemotherapeutic treatments to not take too many antioxidants, as their use could undesirably promote the health of the cancerous cells it is intended to destroy. It follows therefrom that one of ordinary skill in the art *would not* have found it obvious to provide a compound with antioxidant properties in the *treatment* of a cancerous condition, such as skin cancer/melanoma, because one of ordinary skill in the art would not have expected the antioxidant compounds to be effective in the treatment of the cancer, and would even have expected that administration of the anti-oxidant could have undesirable effects.

Exhibits 1-4 attached hereto provide further evidence of the knowledge of those of ordinary skill in the art regarding the undesirability of providing antioxidants for the *treatment* of cancer. Exhibit 1, the article entitled "Use of Antioxidants During Chemotherapy and Radiotherapy Should be Avoided" by Gabrielle M. D'Andrea (hereinafter "D'Andrea") teaches that antioxidants are believed to be likely to protect cancer cells, making their use during cancer treatment highly undesirable (*see, e.g.,* page 6, Abstract and second full paragraph). This article cites, for example, earlier studies where breast cancer patients receiving megadoses of combination vitamins and antioxidants actually showed a trend toward worse survival than controls not receiving the antioxidant dosages (*see, e.g.,* page 320, first full paragraph of right hand column). As discussed above, the reason for such adverse results in the administration of antioxidants to patients suffering from cancer is that while the antioxidants protect and promote the health of normal cells, they also protect and promote the health of cancerous cells, making the eradication of such cancerous cells all the more difficult.

Also, as shown in Exhibit 2 entitled "Antioxidants and Chemotherapy," it is know that most chemotherapy drugs produce "reactive oxygen species" to destroy cancer cells (*see, e.g.,* second full paragraph of Abstract). Conversely, antioxidants can consume the free oxygen radials and thereby counteract the "oxidative" treatment effects on the cancer cells. In other words, the administration of antioxidants to patients being treated for cancer is

undesirable as the antioxidants can undesirably protect the cancer cells from oxidative destruction, negating the effect of the cancer treatment. In fact, the articles set forth in Exhibit 3 provide evidence that cancer cells are capable of upregulating and/or concentrating powerful cellular anti-oxidants such as CoQ10 and vitamin C, to protect themselves from chemotherapeutic drugs. The articles listed in Exhibit 4 further discuss the evidence that antioxidants promote cancer cell health.

Accordingly, it is considered that those of ordinary skill in the art would not find it obvious to provide an antioxidant compound for the *treatment* of cancer, because antioxidants were understood to be likely to actually promote cancer cell health. Thus, in contrast to *preventing or inhibiting* the occurrence of certain types of cancers with antioxidants, the administration of antioxidants for the *treatment* of cancer was understood to be inadvisable because of the undesirable protective effect of the antioxidants on the cancer cells.

In contrast, Applicants have discovered that the compounds as claimed are capable of acting via physiological pathways *other than just antioxidation* to provide *actual treatment* of cancerous conditions, such as skin cancer/melanoma. For example, as described in the instant specification, the compounds as claimed are capable of *treating* various types of cancer by targeting and disrupting the cellular cytoskeleton of the cancer cells, thereby inhibiting the movement and division of the cancer cells (*see, e.g.,* paragraphs [0015]-[0016].) Examples 1-4 of the instant specification give further evidence of the efficacy of the claimed compounds in the treatment of various different types of cancer. This cancer cell targeting and cytoskeleton disrupting activity of the claimed compounds was not known in the art, and thus the use of such compounds to treat cancer is considered to be patentable over the prior art.

Finally, Crea does not make up for the deficiencies of Meisner and Cuomo. Crea teaches that olive-derived hydroxytyrosol can be used for the treatment of skin damage, such as the protection of skin damage resulting from exposure to ultraviolet radiation (*see, e.g.,*

Abstract and paragraph [0083]). In the section to which the Examiner refers, Crea teaches that compositions having the hydroxytyrosol can be formulated in different administration forms, such as parenteral, intravenous, etc. (*see, e.g.,* paragraph [0087]). However, Crea also does not teach or suggest providing the compounds having the formula as claimed for the *treatment of cancer*, such as the treatment of skin cancer/melanoma. It is furthermore noted that as Crea teaches the administration of *hydroxytyrosol*, the teachings therein are not readily combinable with those of Meisner and Cuomo that are directed to the administration of a different compound, namely *oleuropein*.

In summary, claim 1 and the claims depending therefrom are patentable over Meisner, Cuomo and Crea because none of the references teaches or suggests providing the compound as claimed for the *treatment* of cancer. In particular, while Meisner teaches that oleuropein can be provided with glucosamine for the treatment of *psoriasis*, Meisner does not teach or suggest the *treatment of cancer* with oleuropein or a related compound. Cuomo teaches that oleuropein has anti-oxidant properties and may help to *prevent breast cancer*, but does not teach or suggest the *treatment* of breast cancer or other types of cancer with oleuropein. Finally, Crea teaches providing *hydroxytyrosol* for the treatment of skin damage, but does not teach or suggest the *treatment* of cancer. Accordingly, a proper *prima facie* case for the rejection of the cancer treatment method recited in the claims has not been made. Furthermore, as discussed above, the *treatment* of cancer is distinguishable from cancer *prevention*, because antioxidant compositions are understood by those of ordinary skill in the art to be unsuitable and undesirable for the treatment of cancer, even though such compositions may have a beneficial effect in the prevention of cancer.

Accordingly, claim 1 and the claims depending therefrom are patentable over Meisner, Cuomo and Crea because the references do not teach or suggest administering compounds having the formula as claimed for *the treatment of cancer*, such as colon cancer, renal adenocarcinoma and/or melanoma. Applicants thus respectfully request that the rejection under 35 U.S.C. 103(a) of claim 1 and the claims depending therefrom, including claims 9-10 and 17-19, be withdrawn.

Regarding claim 3, it is noted that the claim is similar to claim 1 in that it is directed to the inhibiting the growth, motility, invasiveness and metastasis of cancer cells, the cancer cells being selected from the group consisting of colon cancer, renal adenocarcinoma and melanoma, with a compound having the same formula as in claim 1. Accordingly, claim 3 and the claims depending therefrom are considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 3 and claim 10 depending therefrom is respectfully requested to be withdrawn.

Regarding claim 7, it is noted that the claim is similar to claim 1 in that it is directed to *treating cancer*, the cancer being selected from the group consisting of colon cancer, renal adenocarcinoma and melanoma, with a compound that is produced by the hydrolysis of a compound having the same formula as in claim 1. Accordingly, claim 7 and the claims depending therefrom are considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 7 and claim 25 depending therefrom is respectfully requested to be withdrawn.

Regarding claim 8, it is noted that the claim is similar to claim 1 in that it is directed to *inhibiting cancer cell growth*, the cancer cells being selected from the group consisting of colon cancer, renal adenocarcinoma and melanoma, with a compound that is produced by the hydrolysis of a compound having the same formula as in claim 1. Accordingly, claim 8 is considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 8 is respectfully requested to be withdrawn.

Regarding claim 11, it is noted that the claim is similar to claim 1 in that it is directed to *treating cancer*, the cancer being selected from the group consisting of colon cancer, renal adenocarcinoma and melanoma, with a compound having the same formula as in claim 1. Accordingly, claim 11 and the claims depending therefrom are considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 11 and claims 20-24 depending therefrom is respectfully requested to be withdrawn.

Regarding claim 26, it is noted that the claim is similar to claim 1 in that it is directed to *inhibiting cancer cell growth* with a compound produced by the hydrolysis of a compound having the same formula as in claim 1. Accordingly, claim 26 is considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 26 is respectfully requested to be withdrawn.

Regarding claim 27, it is noted that the claim is similar to claim 1 in that it is directed to *treating cancer in a subject in need thereof, the cancer being selected from the groups consisting of leukemia, renal cell adenocarcinoma, breast ductal carcinoma, melanoma and colon cancer*, with a compound having a formula that falls within the scope of the formula recited in claim 1. Accordingly, claim 27 and the claims depending therefrom are considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 27 and claims 30-31 and 33 depending therefrom is respectfully requested to be withdrawn.

Regarding claim 28, it is noted that the claim is similar to claim 1 in that it is directed to *treating cancer in a subject in need thereof*, with a compound having a formula that falls within the scope of the formula recited in claim 1. Accordingly, claim 28 is considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 28 is respectfully requested to be withdrawn.

Regarding claim 29, it is noted that the claim is similar to claim 1 in that it is directed to selectively targeting and delivering an effective amount of a compound to *inhibit the cancerous growth or recurrence of cancer cells*, the cancer cells being selected from the groups consisting of colon cancer, renal adenocarcinoma and melanoma, with a compound having a formula that falls within the scope of the formula recited in claim 1. Accordingly, claim 29 is considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 29 is respectfully requested to be withdrawn.

5. Rejection of Claims 26-28, 30-31 and 33 under 35 U.S.C. 112, First Paragraph

The Examiner rejected claims 26-28, 30-31 and 33 under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claims. In particular, the Examiner asserts that while the specification is enabling for the treatment of specific cancers such as colon cancer, the specification does not reasonably provide enablement for treating a wide variety of cancers (*see, e.g.,* Office Action page 6.) This rejection is respectfully traversed.

Applicants respectfully wish to point out, as discussed above, that claim 27 is being amended herewith to limit the scope of the cancers being treated to only those "selected from the group consisting of leukemia, renal cell adenocarcinoma, breast ductal carcinoma, melanoma and colon cancer" (i.e., only 5 different types of cancers). Claim 30 depending from claim 27 further limits the compound provided to treat these cancers with *the particular compound that is oleuropein* or its enantiomer. Accordingly, claim 27 and claim 30 have been narrowed in scope to the treatment of only a few select cancers, and in the case of claim 30, treatment with only a single compound or its enantiomer. As such, it is considered that one of ordinary skill in the art would understand how to make and use the inventions claimed therein without requiring undue experimentation, as is discussed further below.

Applicants note that the test for whether claims can be considered to be enabled by the specification as originally filed is whether one of ordinary skill in the art would be capable of making and using the invention *without requiring undue experimentation* (MPEP 2164.01, *see, e.g., in re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)).

Claims 27-28, from which claims 30 and 33 depend, are directed to methods of treating cancer, and claim 26 is directed to a method of inhibiting cancer cell growth, by administering one or more of a set of closely related compounds sharing significant common chemical structure, such as oleuropein, which compounds would be understood by those of ordinary skill in the art to have similar physiological treatment effects. With regards to the use of the compounds in the treatment of cancers, in general, it is noted that the specification as originally filed shows that the compounds are capable of acting *via a mechanism that is*

common to cancer cells to disrupt the cellular cytoskeleton of the cancer cells and reduce their motility, growth, and invasiveness. Accordingly, as the compounds do not act via a mechanism that is specific to a particular type of cancer cell, but instead operate according to a *general mechanism* applicable to all cancer cells, it is considered that one of ordinary skill in the art would be capable of using the compounds to treat a wide variety of cancers without requiring undue experimentation.

The disruption of the cellular cytoskeleton is a generally-applicable cancer chemotherapeutic approach that has been used for the development of treatments of a wide variety of cancer types. A quick review of the literature reveals cytoskeleton disrupting drugs to be known to be efficacious and wide-spectrum, with the drugs having been used to treat multiple different types and varieties of cancers. Exhibit 5 is a list of articles describing cytoskeleton disruption chemotherapeutics as a mechanism for the treatment of a wide variety of diverse cancers. The list of cancers showing efficacy in treatment include, for example, childhood leukemia, advanced breast cancer, adult solid tumors, gliomas, lymphoma and leukemia, metastatic Wilm's tumor, medullablastoma with metastases, neuroblastoma, gynecological cancers, refractory reticulum cell sarcoma, testicular tumors, soft tissue sarcoma, and many, many others, with clinical trials data for such treatment also being available. A literature search for only one of these cytoskeleton disruptors shows over 100,000 scientific reports on the efficacy in the treatment of various different types of cancers. Accordingly, it can be seen that the mechanism of cytoskeletal disruption was widely-accepted by those of ordinary skill in the art (medical practitioners and researchers) as being capable of treating a variety of different types of cancers.

However, a problem with prior cytoskeleton disruption chemotherapeutics that is also known in the art is that they were typically highly toxic, with the LD50 for many such chemotherapeutic agents being on the order of cyanide. Thus, while the prior cytoskeleton disrupting compounds were known to be capable of eradicating cancer cells, they were also known to be toxic to the patients, and as such were not suitable for general use. Table 1 below illustrates the relative toxicity of various known chemotherapeutic agents.

Table 1

Substance	LD50 (mg/kg)
Aspirin [oral]	1000 mg/kg
Ibuprofen (Advil) [oral]	636
Caffeine [oral]	192
Cyclophosphamide (chemo) [oral]	144
Nicotine (found in tobacco) [oral]	53
Etoposide (chemo) [IV injection]	15
Paclitaxel (chemo) [IV injection]	12
Taxol (chemo) [IV injection]	12
Cisplatin (chemo) [IV injection]	11
5'-fluorouracil (chemo) [IV injection]	10
Doxorubicin (chemo) [IV injection]	10
Arsenic (rat poison)	8
Cyanide (poison)	6.2
Vincristine and Vinblastine (chemo) [IV inj.]	1-3

In contrast, Applicants have taken this cytoskeleton disruption paradigm of treatment as precedent and have developed cytoskeleton disrupting drugs that actual **lack** toxicity. In this way, Applicants have been able to utilize a well known mechanism for the eradication of cancer cells, without undesirable and excessive toxicity to the patient that might otherwise preclude the more general application of the method.

Applicants wish to note that this approach is different than that taken in conventional cancer chemotherapeutics development, which has at least in the last 20 years screened for cancer drugs that inhibit cancer cell growth pathways. The conventional wisdom regarding such cancer cell growth inhibitors was that the toxicity of chemotherapeutics could be reduced by targeting mechanisms, such as growth pathways, that are predominantly used by

cancer cells as opposed to normal cells. However, as verified by the Examiner's own cited literature, the attempt to develop cancer therapeutics by targeting such cancer growth pathways has largely been a failure, with only a few human trials having been performed out of thousands of compounds screened, and with those compounds that have received FDA approval often only exhibiting temporary treatment effects before drug resistance develops. One reason for the failure of these growth inhibitors to provide reliable and wide-spectrum treatment of cancers is that cancer growth is in fact a redundant system with multiple back-up growth pathways and mechanisms that can be triggered when needed, such as in response to inhibition of a certain pathway. Exhibit 6 illustrates the complexity of some of the known pathways for cancer cell growth. Thus, the targeting of growth pathways for the screening of chemotherapeutic compounds has given the appearance of unpredictability in the art for cancer treatments, because the redundancy of the cancer growth pathways makes their inhibition difficult to predict and control.

Therefore, in seeking to develop the cancer treatment method of the instant invention, Applicants have turned to the previous more predictable wide-spectrum cancer treatment method of cytoskeleton disruption, which mechanism as discussed above was well known in the art. In particular, Applicants have sought to find non-toxic cytoskeleton disruptor compounds that act via this mechanism, by first selecting "non-toxic" compounds, as assessed by their LD50 values, and screening said compounds for their ability to disrupt the cytoskeleton. It was via this screening that the compounds of Formula I, and in particular oleuropein, were discovered as potent cellular cytoskeleton disruptors. Oleuropein does not have a determinable LD50, and did not illicit lethality even at a dosage of 1000 mg/kg, as described in Exhibit 7. Mechanistically speaking, oleuropein targets the cellular cytoskeleton, which is a substantially non-redundant and conserved system that, as described above, has been known to very predictable in the eradication of cancer cells for 50+ years. All cancer cells regardless of their tissue source need their cytoskeleton for normal physiological activity. In particular, Applicants refer the Examiner to Exhibit 8, the article entitled "Oleuropein as a Non-Toxic Cytoskeleton Disruptor," for a discussion in greater detail about the mechanistic action of oleuropein and related compounds. Thus, Applicants

have taken a previously known mechanism of action for cancer therapeutics, and have screened for a compound having very low toxicity that acts via this mechanism, thus rendering treatment via the mechanism practicable for a wide variety of cancers.

Furthermore, as is described in the article of Exhibit 8, it is believed that compounds such as oleuropein are capable of targeting cancer cells, while remaining substantially non-toxic to normal cell, at least in part because of the glucose moiety that forms a part of the oleuropein compound, as seen for example in claims 30 and 33. As is shown in the article of Exhibit 9, cancer cells are known to up-regulate their glucose transporters, and thus also allow more glucose to enter the cells as compared to normal cells, which is likely due to increased energy utilization of cancer cells. This has been medically proven through the use of PET scans, one of the most sensitive and effective ways of identifying cancers in the body, in which radioactive, fluoridated glucose (FDG) is given to a patient, which FDG is selectively taken up in tumors allowing for their detection. Such PET scan methods are described further in Exhibit 10. Thus, without being limited by any theory, it is believed that oleuropein and related compounds are capable of selectively targeting tumor cells as a result of the increased uptake of the compounds via the glucose moiety in comparison to normal cells.

Accordingly, as the compounds as claimed operate via a mechanism known in the art to be general to all cancers, and are known to have a low toxicity, it is considered that one of ordinary skill in the art would be capable of practicing the cancer treatment methods of the invention without being required to perform undue experimentation. That is, one of ordinary skill in the art would have a reasonable expectation the cancer treatment would work by administering claimed compounds without requiring undue experimentation to determine toxicity levels, etc. The ability to treat without requiring undue experimentation can particularly be seen in the case of the treatment of leukemia, renal cell adenocarcinoma, breast ductal carcinoma, melanoma and colon cancer, for which treatment has been particularly shown in at least Figure 5 of the instant specification.

The Examiner argues that there is no one drug that is capable of treating a wide variety of cancers, and thus performing the methods of the invention would require undue experimentation on the part of those of ordinary skill. Applicants respectfully disagree with this argument, and note that a showing that the compounds can act via a mechanism that is common to all cancers, such as by disrupting the cellular cytoskeleton of the cancer cells, is considered to be sufficient to show enablement of the claimed methods. To draw an analogy to other medical conditions, since it is known that serotonin re-uptake inhibitors are capable of treating depression, a compound that exhibits this biochemical activity would be understood to have a reasonable expectation of being capable of treating depression, even in the absence of human studies proving their efficacy. Thus, methods using such compounds would be considered to be enabled to those of ordinary skill in the art and not requiring undue experimentation.

As further evidence of the compounds' general action on cancer cells, Applicants respectfully direct the Examiner to Example 4 of the instant specification. This example shows oleuropein's effect on the cellular cytoskeleton of cancer cells by a tube-disruption assay. The oleuropein induces cytoskeletal re-organization that "rounds-up" the cells, thereby disrupting the tubular network. The thus rounded cells don't move and remain in place indefinitely, thereby inhibiting motility of the cells. A comparison of Figures 6A and 6B also shows the difference between untreated cells and cells that have been treated with oleuropein, in terms of the tube collapse by disruption and the rounding of the cells. Examples 1-3 further show the effects of oleuropein on cancer cell invasiveness and cancer cell growth. Accordingly, the specification as originally filed demonstrates that oleuropein and like compounds act to treat cancer by disruption of the cellular cytoskeleton of cancer cells. As the disruption of the cellular cytoskeleton is a mechanism common to cancer cells in general, it is considered that one of ordinary skill in the art would be capable of using the claims compounds to treat a wide variety of cancers without requiring undue experimentation.

It is furthermore noted that Figure 5 shows that anti-cancer activity of oleuropein on five different types of very distinct cancers, namely leukemia, renal cell adenocarcinoma, breast ductal carcinoma, melanoma and colon cancer. These cancers represent a wide variety of different cancer types in that they include both tumor-forming and non-tumor forming cancers, are understood to have differing etiologies and affect different physiological systems, and are treated according to different treatment regimens. For example: leukemia is a cancer of the blood or bone marrow often treated by chemotherapeutic methods; colon cancer typically involves cancerous growths (tumors) in the colon and is treated by surgical methods as well as chemotherapy; breast ductal carcinoma is a neoplasm of the breast ducts; and melanoma is a cancer of the skin attributable to genetic factors and excessive exposure to the sun, which is treated by surgery and if necessary by chemotherapeutic and radiation therapy methods. Regardless of the very different natures of these different cancers, it has been demonstrated by Applicants that oleuropein is nonetheless capable of inhibiting the growth of all of these very distinct types of cancer by disrupting the cellular cytoskeletons of the cancer cells, as is shown in Figure 5. This study thus provides further confirmation of the ability of oleuropein and like compounds to treat cancer, and therefore further enables one of ordinary skill in the art to perform the claimed methods without requiring undue experimentation. Applicants further note that Exhibit 8 previously discussed above also provides examples of the efficacy of the claimed compounds in the treatment of cancer.

Applicants further wish to direct the Examiner to Exhibit 11, which demonstrates the efficacy of the claimed compounds in Applicants' own clinical tests in human patients. Applicants note that these tests are not comprehensive of all such studies performed, and as such are intended only to provide a representative sample of the superior treatment results achieved with the claimed method. The first page of Exhibit 11 shows the results for the treatment of a 53 year old male with prostatic adenocarcinoma, with a metastasis on the right symphysis pubis. The claimed compound was administered orally for 8+ months without reported side effects. PSA levels dropped substantially by week 6, and by the 8th month a new bone-scan showed the disappearance of the pubic metastasis. The PSA score also remained low at the 8th month. The second page of Exhibit 11 shows results for the

treatment of a 63 year old female with a breast tumor that had metastasized to multiple lymph nodes, and biopsy confirmed the diagnosis of invasive carcinoma. Administration of the claims compound for one month resulted in what appeared to be complete reduction of the tumor as measured by ultrasound and mammogram,. The third page of Exhibit 11 shows results for the treatment of a 63 year old male having a metastatic tumor in the liver and lymph nodes. Although conventional chemotherapeutic treatment was slightly effective, the cancer growth and increased activity was observed in five hepatic masses upon termination of the conventional treatment. In contrast, administration of the claimed compound for four months resulted in a decrease in tumor size and activity.

Further beneficial results in the treatment of various different types of cancers using the compounds as claimed are described on the fourth page of Exhibit 11. In these examples, administration of the test compound (oleuropein) resulted in the substantial reduction of various different types of tumors in individuals, including reduction of osteosarcoma, breast carcinoma, pancreatic tumors, glioblastoma, and inhibition of recurrence of ductal carcinoma. Thus, administration of the claimed compound provides demonstrably good results in the treatment of a wide variety of different cancers, due to its action via a generally-accepted cancer cell eradication pathway and its very low to negligible toxicity.

Accordingly, it is shown that Applicants have in fact been able to effect treatment of a wide variety of different cancer types with the compounds as claimed, thus providing further verification that the compounds act via a mechanism that is general to all cancer cells, and that is capable of selectively targeting the cancer cells substantially without toxicity to normal cells. The discovery of this wide-spectrum cancer treatment compound thus represents and extraordinary treatment option that represents a substantial advance over prior cancer treatment methods which can be highly toxic and even life-threatening to patients receiving them. Furthermore, Applicants note that as the method utilizes a compound that can be readily extracted from the olive tree, the method improves the accessibility of cancer treatment to the general population. Accordingly, Applicants believe that the method as

claimed represents a significant improvement in cancer treatment that more than meets the requirements for patentability.

Accordingly, claims 26-28, 30 and 33 are considered to be enabled by the originally filed specification for the methods recited therein, and the rejection of these claims under 35 U.S.C. 112, first paragraph, is respectfully requested to be withdrawn.

Conclusion

Applicant respectfully submits that each and every pending claim of the present invention meets the requirements for patentability under 35 U.S.C. §§ 103 and 112, and respectfully requests that the Examiner indicate allowance of each and every pending claim of the present invention.

In view of the foregoing, it is submitted that the Section 103 and 112 rejections have been overcome. Applicant respectfully submits that the amendments to the claims have rendered the Examiner's rejections moot and have placed the claims in a condition for allowance per the Examiner's comments. Accordingly, reconsideration of the outstanding Office Action and allowance of the present application and all the claims therein are respectfully requested and now believed to be appropriate.

If any additional fee is required, please charge Deposit Account Number 19-4330.

Respectfully submitted,

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